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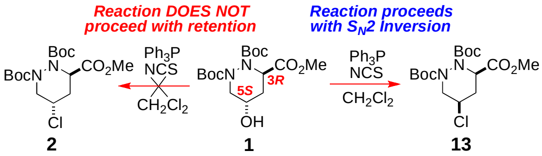

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ABSTRACT

In this paper, an unambiguous synthetic strategy is reported for the preparation of enantiomerically pure *cis*-5-halo-piperazic acid derivatives in single diastereoisomer form. Contrary to the recent report by Shin *et al.* (Ref. 6), in which it is claimed that the Ph_3P and *N*-chlorosuccinimide (NCS)-mediated chlorination of (3*R*,5*S*)-*trans*-*N*(1),*N*(2)-di-*t*-Boc-5-hydroxy-piperazic acid derivative **1** proceeds with retention of configuration at C(5) to give **2**, we now show that this and related Ph_3P-mediated halogenations all occur with S_N2 inversion at the alcohol center, as is customary for such reactions. Specifically, we demonstrate that the (3*R*,5*S*)-*trans*-5-Cl-piperazic acid derivative **2** claimed by Shin *et al.* (Ref. 6) is in actual fact the chlorinated (3*S*,5*R*)-enantiomer **6**, which must have been prepared from the *cis*-(3*S*,5*S*)-alcohol **3**, a molecule whose synthesis is not formally described in the Shin paper. We further show here that the *cis*-(3*R*,5*R*)-5-Cl-Piz **13** claimed by Shin *et al.* in Ref. 6 is also (3*S*,5*R*)-*trans*-5-Cl-Piz **6**. Authentic **13** has now been synthesized by us, for the very first time, here. Since Lindsley and Kennedy have recently utilized the now invalid Shin and coworkers' retentive Ph_3P/NCS chlorination procedure on **1** in their synthetic approach to piperazimycin A (Ref. 10), it follows that their claimed 5-Cl-Piz-containing dipeptide **25** probably has the alternate structure **26**, where the 5-Cl-Piz residue has a 3,5-*cis*-configuration. The aforementioned stereochemical misassignments appear to have come from a mix-up of starting materials by Shin *et al.* (Ref. 6), and an under-appreciation of the various steric and conformational effects that operate in *N*(2)-acylated piperazic acid systems, most especially rotameric $A^{1,3}$-strain. The latter has now been unambiguously delineated and defined here under the banner of the **$A^{1,3}$- rotamer effect**.

Configurational isomers of 5-chloro- and 5-bromo-piperazic acid have been encountered in Nature in many biologically-interesting cyclodepsipeptide natural products. These include the piperazimycins,[1] the kutznerides,[2] the monamycins,[3] and the bromomonamycins[4] to name but a few (Fig 1). In light of this, there has been substantial interest in the chemical synthesis of halogenated piperazic acid derivatives, most especially the enantiopure *trans*-5-chloro-piperazic acid (5-Cl-Piz) variants.[5-11] Our own synthetic effort in this area began in the period 1998-2000, when we first successfully applied our tandem asymmetric electrophilic hydrazination-nucleophilic cyclization technology to stereoselective construction of (3*S*,5*R*)- and (3*R*,5*S*)-*trans*-5-

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Dedicated with fondness, friendship and admiration to the memory of a true maestro of our art, Professor Harry H. Wasserman.

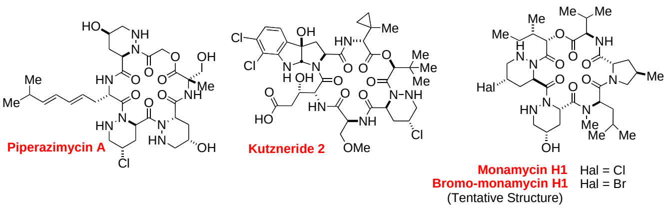
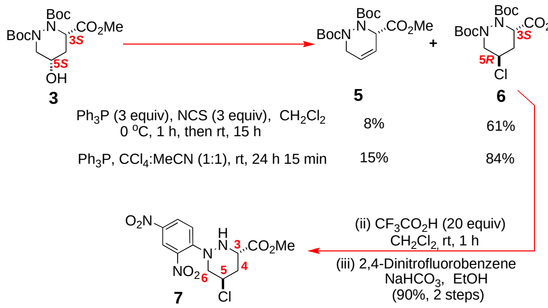
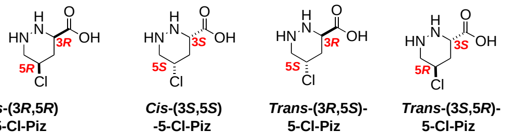


Figure 1. 5-Halo-piperazic acid-containing natural products.



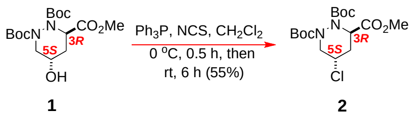
Scheme 1. Ph_3P-mediated chlorinations of **3**.

chloropiperazic acids, as part of our monamycin H1 total synthesis programme.[5]

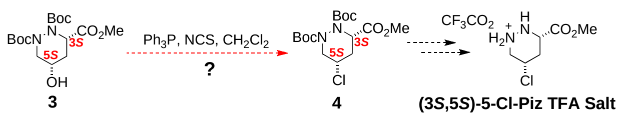


More recently the Hale group has worked with the Walsh and Schroeder teams, to synthesize several *trans*-(3*S*,5*R*)-5-Cl-Piz reference standards that have helped provide powerful new insights into the biosynthetic origins of the kutznerides.[9] Specifically, a thioacyl carrier-bound peptide was identified on the biosynthetic path to the kutznerides that contains a *cis*-5-Cl-Piz-residue.[9] This is then epimerized by an, as yet, undetermined mechanism to produce the *trans*-(3*S*,5*R*)-5-Cl-Piz unit found in the natural products themselves.[9]

As a consequence of these efforts, it was deemed desirable to have synthetic access to a variety of different 3,5-*cis*-5-Cl-Piz derivatives for further studies in this area and, with this in mind, we were drawn to the 2001 report of Shin and coworkers[6] in which it was claimed that the (3*R*,5*S*)-Piz alcohol **1** could be ***retentively*** chlorinated with Ph_3P and *N*-chlorosuccinimide in CH_2Cl_2, to obtain the (3*R*,5*S*)-5-chloride **2**.

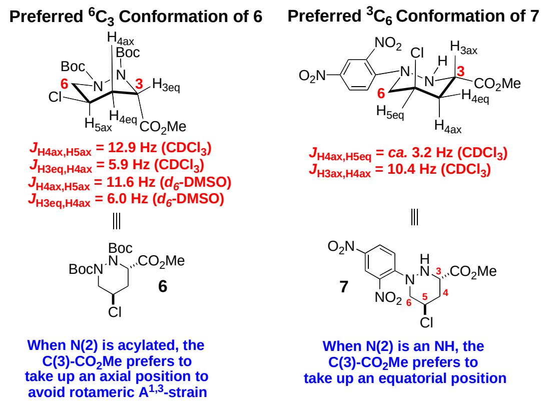


If such a transformation was indeed possible (and subsequent work by Lindsley and Kennedy[10] appeared to suggest that it was), we believed that we might be able to gain rapid access to our desired (3*S*,5*S*)-*cis*-configured chloride **4** from the *cis*-configured (3*S*,5*S*)-alcohol **3**, previously prepared by our team,[5] so obviating the need to develop a completely new synthetic route.

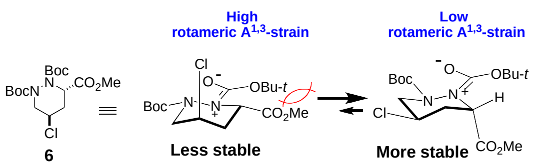


We therefore re-synthesized the known (3*S*,5*S*)-alcohol **3** from D-mannitol by our 1998 route[5] and we examined its chlorination with NCS/Ph_3P in CH_2Cl_2 at rt and, not too surprisingly in hindsight, we observed that chlorination did *not* proceed with retention of configuration, *but with clean* S_N2 *inversion*, as is customary for such chlorination reactions (Scheme 1).[12] Specifically, the process afforded the *trans*-configured chloride **6** that had previously been synthesized by us[5] in 61% yield, alongside a small quantity (8%) of the 4,5-cycloalkene **5**.[5] The latter arose from an *anti*-E2 elimination of the axial H4 and O-chlorophosphorane groups in the $^6C_3$ chair conformation, where the C(3)-carboxymethyl is axial.

Despite the fact that the ^1H NMR spectrum of chloride **6** was rather poorly resolved at 400 MHz in $CDCl_3$, due to the existence of urethane rotamers, the two signals for H4 were relatively sharp and allowed extraction of key coupling constants (see the Supporting Information, SI). Specifically, there was a large apparent td for the $H4_{ax}$ resonance at δ 1.81, which allowed the following *J* values to be determined: $J_{H3eq,H4ax}$ = 5.9 Hz, $J_{H4ax,H5ax}$ = 12.9 Hz and $J_{H4ax,H4eq}$ = -12.9 Hz. Likewise, in d_6-DMSO, the H4ax resonance appeared at δ 1.85 as a well resolved ddd with vicinal coupling constants $J_{H4ax,H5ax}$ = 11.6 Hz and $J_{H3eq,H4ax}$ = 6.0 Hz. The magnitudes of these various coupling constants were all consistent with H-4ax and H5 being antiperiplanar, and H3 sitting equatorially within a $^6C_3$ chair conformation that placed the C(3)-carboxymethyl axial and the C(5)-Cl equatorial.

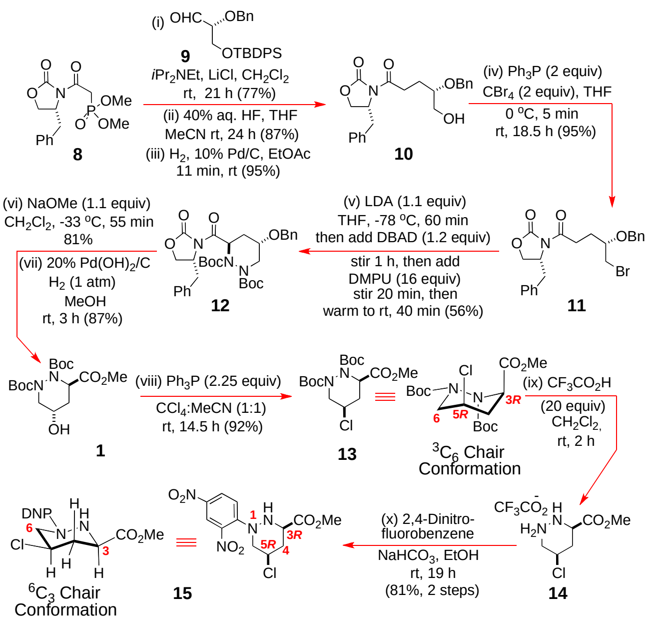


So why should this particular chair conformation be so readily adopted by **6** when the A-value for a carbomethoxy group (1.27) is so much larger than that of a chloride (0.43)?[13] The answer lies in the significant rotameric allylic $A^{1,3}$ strain that arises between the bulky *N*(2)-Boc OBu-*t* substituent and the vicinal C(3)-carboxymethyl substituent, when the latter is equatorial. Indeed, the effect is so pronounced and destabilizing in this particular system that it actually causes the piperazic acid ring to flip into the chair conformation that places the adjacent α-carboxymethyl substituent axial and H3 equatorial.[1] In the case of an *N*(1)/*N*(2) doubly *N*-acylated piperazic acid derivative like **6**, such rotameric strain is further exacerbated by the multiple competing C=N rotameric equilibria that actually exist and the substantial bulk of the two adjacent *N*-Boc groups.



It should be no surprise therefore to find that *N*(2)-substituted-piperazic acid residues within various cyclodepsipeptide natural products are typically associated with an axial C3-carboxamide group; a fact that has long been appreciated by the *cogniscenti* of the cyclodepsipeptide field since the early 1970s, but which has never been quite so explicitly stated or explained previously. Similar arguments hold for *N*(2)-acyl *N*(1)-dehydropiperazic acid-containing cyclodepsipeptides such as the luzopeptins, where the C3-carboxamide again prefers to sit pseudoaxially.[14] We now term this general phenomenon, **the $A^{1,3}$ rotamer effect**, due to it describing a special hidden type of allylic $A^{1,3}$ strain[15] that derives from a dynamic exocyclic rotameric C=N double bond interacting with a substantially sized adjacent "pseudoallylic" substituent. An identical type of $A^{1,3}$-strain has previously been recorded by Johnson for α-functionalized *N*-acyl piperidines.[15]

Notwithstanding the unambiguous structural assignment that we had made for **6**, obtained via the NCS/Ph_3P method, we decided to further secure our assignment. Thus **6** was converted into the *N*(1)-(2'4')-dinitrophenyl-(3*S*,5*R*)-5-chloro-piperazic acid methyl ester **7** by trifluoroacetic acid-induced Boc-cleavage in CH_2Cl_2, and subsequent *N*(1)-alkylation with 2,4-dinitro-fluorobenzene, in EtOH containing sodium bicarbonate; the two steps proceeded in 81-89% overall yield. Compound **7** had a very well resolved 400 MHz ^{1}H NMR spectrum in $CDCl_3$ (see the SI) and, importantly, removal of the *N*(2)-Boc group now led to the $^3C_6$ chair conformation becoming dominant, wherein the C(3)-carboxymethyl was equatorial and the C(5)-Cl was axial, as anticipated based solely on A-values. Evidence for this assignment came from the broadened axial H4 ddd at δ 2.12 which had *J* values of -13.6, 10.4 and 2.6 Hz respectively. The equatorial H(4) resonance also appeared as a ddd at δ 2.29. Its multiplicity readily allowed the geminal H_{4ax}/H_{4eq} coupling constant to be estimated as *ca.* -13.8 Hz. In addition, the H-5 signal at δ 4.55 appeared as a broadened apparent quintet with a *J* value of approximately 3.7 Hz, which indicated that this proton was equatorial and the C(5)-chloride substituent was axial. Collectively, these *J* values meant that $J_{H3ax,H4ax}$ had to be 10.4 Hz and that the averaged $J_{H4ax,H5eq}$ was *ca.* 3.2 Hz. Together, these *J* values confirmed the 3,5-*trans*-relative configuration for this isomer within a $^3C_6$ chair, which is what one would expect after the *N*(2)-acyl substituent had been removed (*vide infra*).



Scheme 2. Our unambiguous synthesis of (3*R*,5*R*)-*Cis*-5-Cl-piperazic acid derivatives.

We next examined the Ph_3P/CCl_4/MeCN mediated chlorination of the *trans*-configured (3*R*,5*S*)-configured alcohol **1**, claimed to have been studied by Shin *et al.*[6] in their paper. In our case, we independently synthesized **1** via a completely new and unambiguous route that was adapted from our earlier work (Scheme 2).[5,9] Importantly, we found that the 3,5-*trans*-alcohol **1** underwent a *clean S_N2 inversion of configuration when submitted to the aforementioned chlorination conditions*, to give the desired 3,5-*cis*-chloride **13** as the *sole* reaction product in 92% yield.[5,9]

Yet again, extensive line broadening was evident for many of the resonances in the ^{1}H spectra of **13**, recorded in a range of NMR solvents (see SI). Fortunately, however, the 400 MHz ^{1}H NMR spectrum of **13** in $CDCl_3$ did give rise to a reasonably well resolved apparent quintet for H-5 at δ 4.19, for the major chair conformer present in solution; it had a *J* value of *ca.* 3.1 Hz, which suggested that a $^3C_6$ chair was being adopted in which the C(5)-Cl was axial. The axial H-4 atom of this major conformer also resonated as a broadened ddd at δ 2.19; it had approximate *J* values of -14.2 ($J_{H4ax,H4eq}$), 6.8 ($J_{H4ax,H3eq}$), and 3.4 Hz ($J_{H4ax,H5eq}$). The latter observations were only compatible with a slightly flattened chair in which H(3) was essentially equatorial and the C(3)-carboxymethyl was essentially axial, as one would expect from the combined operation of the rotameric $A^{1,3}$ effect and N-inversion.

The alternative minor chair conformer could also be detected in this 7:1 mixture of chair conformers. Significantly, the H-4ax resonance for the minor chair conformer appeared as a large apparent quartet of overall width 36 Hz. This argued that three large and fairly similar *J* values were contributing to the overall splitting. It also confirmed that this minor conformer was the alternative *cis*-3,5-configured $^6C_3$ chair in which the C(3)-carboxymethyl and C(5)-Cl were now both equatorial. Presumably this minor chair conformer is observable for **13** because of the significant 1,3-diaxial interaction that exists across the ring when these substituents are both axial.

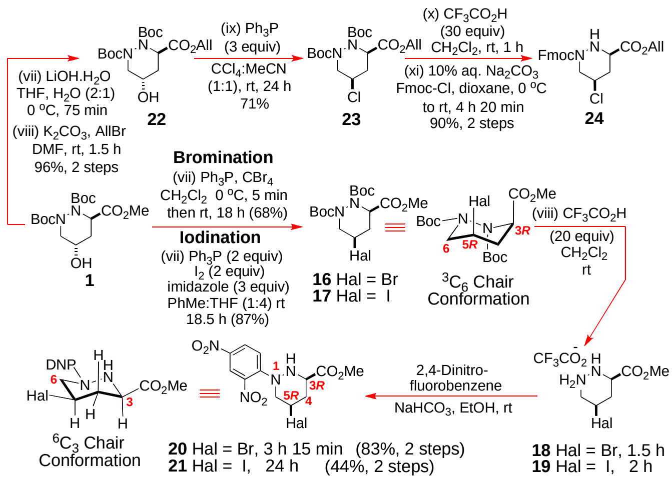
Even so, to place our absolute stereochemical assignment beyond any doubt at all, we converted **13** into the *cis*-configured *N*(1)-(2'4')-dinitrophenyl (3*R*,5*R*)-5-chloro-piperazic acid methyl ester derivative **15** (Scheme 2). 400 MHz ^{1}H NMR spectroscopy of **15** in $CDCl_3$ now very clearly revealed that the all *cis*-configured (3*R*,5*R*)-5-Cl-Piz derivative had indeed been prepared (see SI). Specifically it showed that the $^6C_3$ chair conformation was now being adopted in which the C(3)- and C(5)-substituents were both equatorial. This assignment was secured by the large diaxial coupling constants observed for $J_{H4ax,H5ax}$ and $J_{H5ax,H6ax}$. In this regard, the signal for the axial H-4 proton at δ 1.73 was an apparent quartet with fairly broad lines, even on heating to 50 °C. The width of this apparent quartet was 36.3 Hz demonstrating that three large coupling constants of roughly similar magnitude (*ca.* 12.1 Hz) were contributing to the splitting. The partnering H(4) equatorial peak was a doublet of apparent triplets at δ 2.61, which allowed estimation of the geminal coupling constant as -12.4 Hz. Therefore the sum of the two vicinal coupling constants in the axial H4-multiplet was 23.9 Hz, but due to the broadness of the signals (line width 3 Hz), these two values could not be determined with precision. Nonetheless, spectral simulation revealed that a difference in vicinal coupling constant of 2.6 Hz could be identified in the measured spectra so that the other two *J* values had to be *ca.* 11.95 Hz (± 1.3 Hz). All values in this range are consistent with diaxial coupling which proved that the relative configuration of **15** must be *cis*, with the chloro and carbomethoxygroups both occupying equatorial positions.

A careful re-examination and comparison of Shin and coworkers' reported spectral and optical rotation data for their claimed (3*R*,5*S*)-*trans*-**2**,[6] with our own data for the (3*S*,5*R*)-

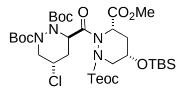
trans-**6** enantiomer, reveals that Shin and coworkers have actually prepared (3*S*,5*R*)-*trans*-**6**, rather than the (3*R*,5*S*)-*trans*-**2** claimed in their paper,[6] and our combined halogenation studies prove that the former must have originated from the (3*S*,5*S*)-*cis*-configured alcohol **3**, *whose synthesis has not been formally described by Shin et al. in reference 6*. In addition, the spectral and $[\alpha]_D$ data that Shin *et al.* report for the *cis*-3,5-chloride **13** are irreconcilable with the 3,5-*cis* stereochemistry that they claim. They also do not match with the NMR data that we have independently obtained for authentic **13** in d_6-DMSO (see our SI).[6] Indeed, the ^{1}H NMR spectrum and $[\alpha]_D$ measurement for their claimed *cis*-(3*R*,5*R*)-5-Cl-Piz derivative **13** appear to more reasonably agree with the data for the (3*S*,5*R*)-*trans*-chloride **6** that we have synthesized from **3** by the Ph_3P/NCS and Ph_3P/CCl_4/MeCN methods (see our SI for the spectral comparison).[5] The *cis* (3*R*,5*R*)-5-Piz chloride **13** that the Shin group have laid claim to, has, in our opinion, simply not been prepared by this team. Our present report thus constitutes the *first* unambiguous total synthesis of an enantiopure 3,5-*cis*-configured 5-chloro-Piz derivative that has knowingly been synthesized.

Since a number of bromomonamycin natural products[4] are also now known, we considered it important that we definitively synthesize the *cis*-5-bromo- and 5-iodo-piperazic acid derivatives **16** and **17**, via our approach (Scheme 3), to place their stereochemical assignments on a secure footing. Our results are presented below. The key point that we wish to make here is that the Ph_3P-mediated bromination and iodination processes on **1** (including that with Ph_3P/NIS; see SI) both proceed with S_N2 inversion of configuration, as one would expect. Likewise, inversion was also observed in the Ph_3P/CCl_4/MeCN mediated chlorination of **22** to obtain **23**, which was thereafter converted into **24**.

Scheme 3. Our unambiguous synthesis of various (3*R*,5*R*)-*Cis*-5-halogeno-piperazic acid derivatives.



Given the stereochemical misassignments of Shin *et al.*,[6] this does of course mean that the recently published synthetic work of Lindsley and Kennedy[10] on piperazimycin A must now be fully reexamined and possibly revised, since these workers have unsuspectingly relied upon the now defunct Shin retentive Ph_3P/NCS chlorination of **1**[6] in their claimed synthesis of the dipeptide **25**. In light of the problems that we have identified, it would appear that Lindsley and Kennedy[10] have most likely synthesized the dipeptide **26** rather than **25**. However, we cannot be absolutely certain of this presently due to the lack of *J* values and multidimensional NMR assignments in their report.[10]



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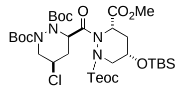

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In conclusion, we have now demonstrated that the tandem asymmetric electrophilic hydrazination-nucleophilic cyclization method developed in our laboratory[5,9] for piperazic acid synthesis can successfully be applied for the stereocontrolled synthesis of either 3,5-*cis*- or 3,5-*trans*-5-halo-piperazic acid derivatives in enantiopure form. We have also proven that *N*(1), *N*(2) or C(3)-CO_2Me mediated neighboring-group participation does *not* occur in the Ph_3P-mediated halogenation of 5-hydroxy-*N*(1),*N*(2)-di-*N*-acylated piperazic acid derivatives, *nor* do these substitutions proceed via the S_Ni mechanism. Indeed, such reactions always proceed with stereochemical inversion,[12] as was indicated in our 1998,[5] 2000[5] and 2011[9] literature reports. We have also provided here, for the very first time, an unambiguous explanation of how the rotameric $A^{1,3}$-effect can dramatically affect piperazic acid ring conformation in *N*(2)-acyl piperazic acid derivatives,[16] and we have definitively shown how this effect can force the adoption of a seemingly disfavored chair that places the C(3)-carboxy in an axial orientation. Similar effects undoubtedly operate in related systems such as *N*-acyl pipecolic acids.[15] We hope that our latest work will now restore clarity to the area of 5-hydroxy-Piz halogenation[5,9] which had become rather muddled[6,10] following the publications of Shin *et al.*[6] and Lindsley and Kennedy.[10]

Acknowledgments

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Supplementary Material

Copies of the 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra are supplied for all the new and previously unreported intermediates described in this route.